What is claimed is:

1. A method for obtaining a focused library of candidate binding compounds for a protein family, wherein the members of the protein family bind a common ligand, comprising the steps of:

(a) observing competitive binding of the common ligand and a first ligand to a protein, wherein the protein is a member of the protein family, thereby determining that the first ligand binds to the common ligand binding site of the protein;

(b) providing a sample comprising the protein, the first ligand and a second ligand under conditions wherein the first ligand, the second ligand and the protein form a bound complex;

c) detecting a subset of magnetization transfer signals between the first ligand and the second ligand in the bound complex, wherein the signals are obtained from an isotope edited NOESY spectrum of said sample; thereby determining that the two ligands are proximal in the bound complex; and

(d) obtaining a population of candidate binding compounds comprising the first ligand, or a fragment thereof, linked to one of a plurality of second ligand homologs,

whereby the population contains binding compounds that bind to members of the protein family.

2. The method of claim 1, wherein the first ligand is identified by a method comprising measuring cross-saturation for a bound complex comprising the first ligand bound to the macromolecule.

3. The method of claim 2, wherein the cross-saturation is measured using WaterLOGSY.

4. The method of claim 1, wherein the first ligand is identified by obtaining a structure model for the binding site of the macromolecule and docking a structure model of the first ligand with the structure model of the binding site.

5. The method of claim 1, wherein step (c) further comprises identifying an atom of the first ligand that is proximal to an atom of the second ligand.

6. The method of claim 5, further comprising determining the distance between the atom of the first ligand that is proximal to the atom of the second ligand.

7. The method of claim 6, wherein the linker connects the first ligand, or fragment thereof, and the second ligand homolog such that the first ligand, or fragment thereof can be separated from the second ligand homolog by the distance separating them in the bound complex.

8. The method of claim 7, wherein the linker connects the first ligand and the second ligand homolog at the positions of the proximal atoms of the first and second ligands.

9. The method of claim 1, wherein said NOESY spectrum is a 2D NOESY spectrum.

10. The method of claim 1, wherein said isotope-edited NOESY spectrum is a ^{13}C-edited NOESY spectrum.

11. The method of claim 1, further comprising repeating steps (b) through (d), wherein the first ligand is replaced by the binding compound obtained in step (d) and the second ligand is replaced by another ligand.

12. A method of identifying a compound that binds a protein, comprising the steps of:

(a) obtaining a focused library of candidate binding compounds for a protein family according to claim 1;

(b) assaying the focused library for the ability to bind to a protein, wherein the protein is a member of the protein family; and

(c) identifying a member of the focused library that binds to the protein.

13. A method for refining a compound that binds a protein comprising,

(a) identifying a binding compound that is a member of a focused library according to claim 12;

(b) obtaining one or more modified forms of the second ligand of the binding compound;

(c) providing a sample comprising the protein, the first ligand and a modified second ligand under conditions wherein the first ligand, the modified second ligand and the protein form a bound complex;

(d) detecting a subset of magnetization transfer signals between the first ligand and the modified second ligand in the bound complex, wherein said signals are obtained from an isotope edited NOESY spectrum of said sample; thereby determining that the two ligands are proximal in the bound complex; and

(e) selecting a modified second ligand having increased or decreased proximity to the first ligand with respect to the parent compound that binds a protein.

14. The method of claim 13, wherein said modified second ligand comprises an antenna moiety.

15. A method for obtaining a focused library of candidate binding compounds, wherein the members of the protein family bind a common ligand, comprising the steps of:

(a) providing a plurality of samples comprising the protein and a first ligand under conditions wherein the first ligand and the protein form a bound complex, wherein the protein is a member of a family of proteins that bind a common ligand;

(b) assaying a population of candidate second ligands for the ability to transfer magnetization to the first ligand in a sample from the plurality, wherein said ability to transfer magnetization is assessed by determining a subset of magnetization signals of an isotope-edited NOESY spectrum of said sample;

(c) identifying, from the population of candidate second ligands, a second ligand that transfers magnetization to the first ligand, thereby determining that the two ligands are proximal to each other in a ternary bound complex with the protein;

(d) observing competitive binding between one of the two ligands and the common ligand, thereby determining that the competitive binding ligand binds to the common ligand binding site of the protein; and

(e) obtaining a population of candidate binding compounds comprising the competitive binding ligand, or a

fragment thereof, linked to one of a plurality of homologs of the other ligand,

whereby the population of candidate binding compounds contains binding compounds that bind to members of the protein family.

16. The method of claim 15, wherein the population of candidate second ligands comprise a MOTIF library.

17. The method of claim 15, wherein the first ligand is identified by a method comprising measuring cross-saturation for a bound complex comprising the first ligand bound to the macromolecule.

18. The method of claim 17, wherein the cross-saturation is measured using WaterLOGSY.

19. The method of claim 15, wherein the first ligand is identified by obtaining a structure model for the binding site of the macromolecule and docking a structure model of the first ligand with the structure model of the binding site.

20. The method of claim 15, wherein the first ligand is identified by a binding assay.

21. The method of claim 15, wherein said NOESY spectrum is a 2D NOESY spectrum.

22. The method of claim 21, further comprising determining the distance between the atom of the first ligand that is proximal to the atom of the second ligand.

23. The method of claim 22, wherein the linker connects the first ligand, or fragment thereof, and the second ligand homolog such that the first ligand, or fragment thereof can be separated from the second ligand homolog by the distance separating them in the bound complex.

24. The method of claim 23, wherein the linker connects the first ligand and the second ligand homolog at the positions of the proximal atoms of the first and second ligands.

25. The method of claim 15, wherein said isotope-edited NOESY spectrum is a ^{13}C-edited NOESY spectrum.

26. The method of claim 15, wherein step (c) further comprises identifying an atom of the first ligand that is proximal to an atom of the second ligand.

27. The method of claim 15, further comprising repeating steps (a) through (e), wherein the first ligand is replaced by the binding compound obtained in step (e) and the second ligand is replaced by another ligand.

28. A method of identifying a compound that binds a protein, comprising the steps of:

(a) obtaining a focused library of candidate binding compounds for a protein family according to claim 15;

(b) assaying the focused library for the ability to bind to a protein, wherein the protein is a member of the protein family; and

(c) identifying a member of the focused library that binds to the protein.

29. A method for refining a compound that binds a protein comprising,

(a) identifying a binding compound that is a member of a focused library according to claim 27;

(b) obtaining one or more modified forms of the second ligand of the binding compound;

(c) providing a sample comprising the protein, the first ligand and a modified second ligand under conditions wherein the first ligand, the modified second ligand and the protein form a bound complex;

(d) detecting a subset of magnetization transfer signals between the first ligand and the modified second ligand in the bound complex, wherein said signals are obtained from an isotope edited NOESY spectrum of said sample; thereby

determining that the two ligands are proximal in the bound complex; and

(e) selecting a modified second ligand having increased or decreased proximity to the first ligand with respect to the parent compound that binds a protein.

30. The method of claim 29, wherein said modified second ligand comprises an antenna moiety.

31. The method of claim 17, wherein the first ligand is identified by assaying a population of candidate first ligands for the ability to bind the protein and identifying from the population of candidate first ligands a first ligand that binds to the protein.

32. The method of claim 15, wherein the population of candidate first ligands comprise a MOTIF library.

33. A method for obtaining a binding compound having specificity for a member of a protein family, wherein the members of the protein family bind a common ligand, comprising the steps of:

(a) observing competitive binding of the common ligand and a first ligand to a first protein,

(b) observing competitive binding of the common ligand and a first ligand to a second protein,

wherein the first and second proteins are members of the protein family, thereby determining that the first ligand binds to the common ligand binding site of the first and second proteins;

(c) providing a sample comprising the first protein, the first ligand and a second ligand;

(d) providing a sample comprising the second protein, the first ligand and the second ligand;

(e) comparing the degree of magnetization transfer between the first ligand and the second ligand for the samples of parts (b) and (c), wherein magnetization transfer is determined by detecting a subset of magnetization transfer signals from an isotope-edited NOESY spectrum of said sample; and

(f) obtaining a binding compound comprising the first ligand, or a fragment thereof, linked to the second ligand, or a fragment thereof,

whereby the binding compound selectively binds the first protein compared to the second protein.

34. The method of claim 33, wherein the proteins are deuterium labeled.

35. The method of claim 33, wherein the degree of magnetization transfer is determined by measuring cross-saturation.

36. The method of claim 35, wherein the cross-saturation is measured using WaterLOGSY.

37. The method of claim 33, wherein step (e) further comprises identifying an atom of the first ligand that is proximal to an atom of the second ligand.

38. The method of claim 37, further comprising determining the distance between the atom of the first ligand that is proximal to the atom of the second ligand.

39. The method of claim 38, wherein the linker connects the first ligand, or fragment thereof, and the second ligand homolog such that the first ligand, or fragment thereof can be separated from the second ligand homolog by the distance separating them in the bound complex.

40. The method of claim 38, wherein the first ligand, or fragment thereof, and the second ligand, or fragment thereof, are linked at the positions of the proximal atoms of the first and second ligands.

41. The method of claim 33, wherein the first ligand comprises a ligand-probe having an antenna moiety.

42. The method of claim 41, wherein step (e) comprises comparing the degree of magnetization transfer between the antenna moiety of the ligand-probe and the second ligand for the samples of parts (b) and (c).

43. The method of claim 41, wherein the ligand-probe comprises a common ligand attached to the antenna moiety.

44. The method of claim 33, wherein said isotope-edited NOESY spectrum is a ^{13}C-edited NOESY spectrum.

45. The method of claim 33, wherein step (c) further comprises identifying an atom of the first ligand that is proximal to an atom of the second ligand.

46. A method for refining a compound that binds a protein comprising,

(a) identifying a binding compound that is a member of a focused library according to claim 33;

(b) obtaining one or more modified forms of the second ligand of the binding compound;

(c) providing a sample comprising the protein, the first ligand and a modified second ligand under conditions wherein the first ligand, the modified second ligand and the protein form a bound complex;

(d) detecting a subset of magnetization transfer signals between the first ligand and the modified second ligand in the bound complex, wherein said signals are obtained from an isotope edited NOESY spectrum of said sample; thereby determining that the two ligands are proximal in the bound complex; and

(e) selecting a modified second ligand having increased or decreased proximity to the first ligand with respect to the parent compound that binds a protein.

47. The method of claim 45, wherein said modified second ligand comprises an antenna moiety.

48. A method for obtaining a focused library of candidate binding compounds for a protein family, wherein the members of the protein family bind a common ligand, comprising the steps of:

(a) providing a ligand-probe having an antenna moiety, wherein the ligand-probe binds to the common ligand binding site of a protein, wherein the protein is a member of the protein family;

(b) providing a sample comprising the protein, the ligand-probe and a second ligand under conditions wherein the ligand-probe, the second ligand and the protein form a bound complex;

(c) detecting a subset of magnetization transfer signals between antenna moiety of the ligand-probe and the second ligand in the bound, wherein said signals are obtained from an isotope-edited NOESY spectrum of said sample, thereby determining that the antenna moiety and second ligand are proximal in the bound complex; and

(d) obtaining a population of candidate binding compounds comprising the ligand-probe, or a fragment thereof, linked to one of a plurality of second ligand homologs,

whereby the population contains binding compounds that bind to members of the protein family.

49. The method of claim 48, wherein the ligand-probe comprises a common ligand attached to the antenna moiety.

50. The method of claim 49, wherein step (d) comprises obtaining a population of candidate binding compounds comprising the common ligand, or a fragment thereof, linked to one of a plurality of second ligand homologs.

51. The method of claim 49, wherein candidate binding compounds in the population of step (d) have a linkage between the antenna moiety and a second ligand homolog.

52. The method of claim 48, wherein the ligand probe has a plurality of antenna moieties.

53. The method of claim 48, wherein step (d) comprises detecting magnetization transfer between the antenna moieties of the ligand-probe and the second ligand in the bound complex, thereby determining that the antenna moieties and second ligand are proximal in the bound complex.

54. The method of claim 48, further comprising a step of observing competitive binding of a common ligand and the ligand-probe to the protein, thereby determining that the ligand-probe binds to the common ligand binding site of the protein.

55. The method of claim 54, wherein binding of the ligand-probe is identified by a method comprising measuring cross-saturation for a bound complex comprising the first ligand bound to the macromolecule.

56. The method of claim 55, wherein the cross-saturation is measured using WaterLOGSY.

57. The method of claim 48, wherein the protein is deuterium labeled.

58. The method of claim 48, wherein the ligand-probe is identified based on visual inspection of a structure model for the binding site of the macromolecule.

59. The method of claim 48, wherein step (c) further comprises identifying an atom of the antenna moiety that is proximal to an atom of the second ligand.

60. The method of claim 59, further comprising determining the distance between the atom of the antenna moiety that is proximal to the atom of the second ligand.

61. The method of claim 48, wherein said NOESY spectrum is a 2D NOESY spectrum.

62. The method of claim 48, wherein said isotope-edited NOESY spectrum is a ^{13}C-edited NOESY spectrum.

63. A method of identifying a compound that binds a protein, comprising the steps of:

(a) obtaining a focused library of candidate binding compounds for a protein family according to claim 48;

(b) assaying the focused library for the ability to bind to a protein, wherein the protein is a member of the protein family; and

(c) identifying a member of the focused library that binds to the protein.

64. A method for refining a compound that binds a protein comprising,

(a) identifying a binding compound that is a member of a focused library according to claim 63;

(b) obtaining one or more modified forms of the second ligand of the binding compound;

(c) providing a sample comprising the protein, the first ligand and a modified second ligand under conditions

wherein the first ligand, the modified second ligand and the protein form a bound complex;

(d) detecting a subset of magnetization transfer signals between the first ligand and the modified second ligand in the bound complex, wherein said signals are obtained from an isotope edited NOESY spectrum of said sample; thereby determining that the two ligands are proximal in the bound complex; and

(e) selecting a modified second ligand having increased or decreased proximity to the first ligand with respect to the parent compound that binds a protein.

65. The method of claim 64, wherein said modified second ligand comprises an antenna moiety.

66. A method for obtaining a focused library of candidate binding compounds, wherein the members of the protein family bind a common ligand, comprising the steps of:

(a) providing a ligand-probe having an antenna moiety, wherein the ligand-probe binds to the common ligand binding site of a protein, wherein the protein is a member of the protein family;

(b) providing a plurality of samples comprising the protein and the ligand-probe under conditions wherein the ligand-probe and the protein form a bound complex, wherein the protein is a member of a family of proteins that bind a common ligand;

(c) assaying a population of candidate second ligands for the ability to transfer magnetization to the antenna moiety of the ligand-probe in a sample from the plurality, wherein said ability to transfer magnetization is assessed by determining a subset of magnetization signals of a an isotope-edited NOESY spectrum of said sample

(d) identifying, from the population of candidate second ligands, a second ligand that transfers magnetization to the antenna moiety of the ligand-probe, thereby determining that the two ligands are proximal to each other in a ternary bound complex with the protein; and

(e) obtaining a population of candidate binding compounds comprising the ligand-probe, or a fragment thereof, linked to one of a plurality of homologs of the other ligand,

whereby the population of candidate binding compounds contains binding compounds that bind to members of the protein family.

67. The method of claim 66, wherein the ligand probe comprises a common ligand attached to the antenna moiety.

68. The method of claim 66, wherein step (e) comprises obtaining a population of candidate binding compounds comprising the common ligand, or a fragment thereof, linked to one of a plurality of second ligand homologs.

69. The method of claim 66, wherein candidate binding compounds in the population of step (e) have a linkage between the antenna moiety and a second ligand homolog.

70. The method of claim 66, wherein the ligand probe has a plurality of antenna moieties.

71. The method of claim 70, wherein step (c) comprises assaying a population of candidate second ligands for the ability to transfer magnetization to the plurality of antenna moiety of the ligand-probe in a sample from the plurality.

72. The method of claim 66, further comprising a step of observing competitive binding of a common ligand and the ligand-probe to the protein, thereby determining that the ligand-probe binds to the common ligand binding site of the protein.

73. The method of claim 72, wherein binding of the ligand-probe is identified by a method comprising measuring cross-saturation for a bound complex comprising the first ligand bound to the macromolecule.

74. The method of claim 73, wherein the cross-saturation is measured using WaterLOGSY.

75. The method of claim 66, wherein the protein is deuterium labeled.

76. The method of claim 66, wherein the ligand-probe is identified based on visual inspection of a structure model for the binding site of the macromolecule.

77. The method of claim 66, further comprising determining that the second ligand binds to a different location on the protein from the common ligand.

78. The method of claim 66, wherein step (d) further comprises identifying an atom of the antenna moiety that is proximal to an atom of the second ligand.

79. The method of claim 78, further comprising determining the distance between the atom of the antenna moiety that is proximal to the atom of the second ligand.

80. The method of claim 66, wherein said NOESY spectrum is a 2D NOESY spectrum.

81. The method of claim 66, wherein said isotope-edited NOESY spectrum is a ^{13}C-edited NOESY spectrum.

82. A method of identifying a compound that binds a protein, comprising the steps of:

(a) obtaining a focused library of candidate binding compounds for a protein family according to claim 66;

(b) assaying the focused library for the ability to bind to a protein, wherein the protein is a member of the protein family; and

(c) identifying a member of the focused library that binds to the protein.

83. A method for refining a compound that binds a protein comprising,

(a) identifying a binding compound that is a member of a focused library according to claim 82;

(b) obtaining one or more modified forms of the second ligand of the binding compound;

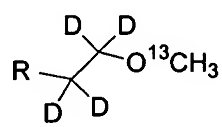
(c) providing a sample comprising the protein, the first ligand and a modified second ligand under conditions wherein the first ligand, the modified second ligand and the protein form a bound complex;

(d) detecting a subset of magnetization transfer signals between the first ligand and the modified second ligand in the bound complex, wherein said signals are obtained from an isotope edited NOESY spectrum of said sample; thereby determining that the two ligands are proximal in the bound complex; and

(e) selecting a modified second ligand having increased or decreased proximity to the first ligand with respect to the parent compound that binds a protein.

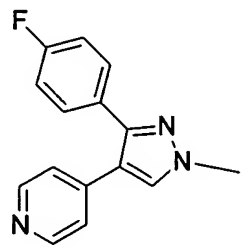
84. The method of claim 83, wherein said modified second ligand comprises an antenna moiety.

85. A compound of the formula:



wherein R is any chemical moiety which binds to the macromolecular target and where the point of attachment does not influence binding of the ligand by methods which will be familiar to a person skilled in the art (as judged either by NMR direct binding, activity assay or biophysical, spectroscopic method or computational ligand docking into a structural model).

86. A compound of claim 85, wherein R is



87. A method for identifying a ligand that binds to a macromolecular target, comprising the steps of:

(a) attaching an antenna moiety to a first ligand, wherein said ligand binds specifically to a macromolecular target;

(b) providing a sample comprising macromolecular target, the first ligand and a candidate second ligand under conditions wherein the first ligand and the macromolecular target form a bound complex;

(c) detecting a subset of magnetization transfer signals between the antenna moiety of the first ligand and the second candidate ligand, wherein said signals are obtained from an isotope edited NOESY spectrum of said sample; thereby determining that the two ligands are proximal in a bound complex, and identifying a second ligand that binds to said macromolecular target.

88. The method of claim 87 further comprising determining the distance between the atom of the first ligand that is proximal to the atom of the candidate ligand.

89. The method of claim 87, wherein said NOESY spectrum is a 2D NOESY spectrum.

90. The method of claim 87, wherein said isotope-edited NOESY spectrum is a ^{13}C-edited NOESY spectrum.